COMBINATIONS INCLUDING BETA-ADRENORECEPTOR AGONISTS FOR TREATMENT OF PARKINSON`S DISEASE AND MOVEMENT DISORDERS

CLAIM OF PRIORITY

[0001] This application claims the benefit of U.S. Provisional Patent Application Ser. No. 62/487,541, filed on Apr. 20, 2017. The entire contents of the foregoing are hereby incorporated by reference.

FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

[0002] This invention was made with Government support under Grant No. U01 NS082157, U01 NS 095736 and RO1 NS083845 awarded by the National Institutes of Health. The Government has certain rights in the invention.

TECHNICAL FIELD

[0003] The present invention relates to the treatment of neurological disorders (e.g., Parkinson's disease) using drug combinations that include beta-adrenoreceptor agonists with other drugs and health supplements.

BACKGROUND

[0004] Parkinson's disease is a movement disorder that affects one or more muscle groups. Symptoms of Parkinson's disease include: tremors, slowness of voluntary movements, change in gait, and unsteady balance. It is estimated that nearly 10 million people worldwide are living with Parkinson's disease.

SUMMARY

[0005] The present invention is based, at least in part, on the discovery that the β2-adrenoreceptor regulates the transcription of α-synuclein, predicts the risk of Parkinson's disease in a ligand-specific fashion and constitutes a unique target for therapeutic intervention. Copy number mutations implicate excess production of α-synuclein as a possibly causative factor in Parkinson's disease (PD). Using an unbiased screen targeting endogenous gene expression, the β2-adrenoreceptor (β2AR) was discovered as a regulator of the α-synuclein gene (SNCA). β2AR ligands modulate SNCA transcription via histone 3 lysine 27 acetylation of its promoter and enhancers. During 11 years of follow up in four million Norwegians, the β2AR agonist salbutamol, a brain-penetrant asthma medication, was associated with reduced risk of developing PD (rate ratio =0.66, 95% C.I. 0.58-0.76). Conversely, a β2AR antagonist correlated with increased risk. β2AR activation protected model mice and patient-derived cells. Thus, β2AR links to transcription of α-synuclein and risk of PD in a ligand-specific fashion and constitutes a potential target for therapies.

[0006] Provided herein are methods of treating a subject who has a synucleinopathy that include: administering to a subject in need of such treatment therapeutically effective amounts of a β2-adrenoreceptor agonist and at least one therapeutic agent selected from the group consisting of: a synucleinopathy therapeutic agent, a β2-adrenoreceptor antagonist and a health supplement, wherein the health supplement is selected from the group consisting of caffeine, inosine, creatine, coenzyme Q10, vitamin E, and omega-3 fatty acids, to thereby treat Parkinson's disease in the subject.

[0007] In some embodiments of any of the methods described herein, the method further includes identifying the subject as having a synucleinopathy, e.g., Parkinson's disease prior to administering.

[0008] In some embodiments the method includes administering a β2-adrenoreceptor agonist, a synucleinopathy therapeutic agent and at least one of the health supplements.

[0009] In some embodiments, the β2-adrenoreceptor agonist is a blood brain penetrant β2-adrenoreceptor agonist. In some embodiments, the β2-adrenoreceptor agonist is selected from the group consisting of bitolterol, fenoterol, isoprenaline, levosalbutamol, orciprenaline, pirbuterol, procaterol, ritodrine, salbutamol, terbutaline, arformoterol, bambuterol, clenbuterol, formoterol, salmeterol, abediterol, carmoterol, indacaterol, olodaterol, vilanterol, metaproterenol, mabuterol, and zilpaterol. In some embodiments, the β2-adrenoreceptor agonist is selected from the group consisting of salbutamol, metaproterenol, clenbuterol and salbutamol.

[0010] In some embodiments, the synucleinopathytherapeutic agent is selected from the group consisting of levodopa, carbidopa, entacapone, ropinirole, rotigotine, pramipexole, bromocriptine, rasagiline, selegiline, amantadine and trihexphenidyl.

[0011] In some embodiments, the method includes administering a β2-adrenoreceptor agonist and a β2-adrenoreceptor antagonist.

[0012] In some embodiments, the β2-adrenoreceptor antagonist does not penetrate the blood brain barrier.

[0013] In some embodiments, the β2-adrenoreceptor antagonist is selected from the group consisting of carteolol, carvedilol, labetalol, nadolol, penbutolol, pindolol, sotalol, timolol, oxprenolol and butaxamine.

[0014] In some embodiments of any of the methods described herein, the method further includes administering therapeutically effective amounts of riluzole hydrochloride, or a pharmaceutically acceptable salt, prodrug, or isomer thereof.

[0015] In some embodiments, the β2-adrenoreceptor agonist and the at least one therapeutic agent are administered simultaneously to the subject; wherein the β2-adrenoreceptor agonist is administered to the subject prior to administration of the at least one therapeutic agent; or wherein the at least one therapeutic agent is administered to the subject prior to administration of the β2-adrenoreceptor agonist.

[0016] In some embodiments, the subject has Parkinson's disease.

[0017] In some embodiments, the subject does not have Parkinson's disease.

[0018] Provided herein are uses of a β2-adrenoreceptor agonist and a β2-adrenoreceptor antagonist in the manufacture of a medicament for treatment of a synucleinopathy.

[0019] Also provided herein are uses of a β2-adrenoreceptor agonist and a health supplement in the manufacture of a medicament for treatment of a synucleinopathy, wherein the health supplement is selected from the group consisting of caffeine, inosine, creatine, coenzyme Q10, vitamin E, and omega-3 fatty acids.

[0020] The term "therapeutically effective amount" refers to that amount of the β2-adrenoreceptor agonist and/or the therapeutic agent being administered sufficient to treat a